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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1627	
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12/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,761	HARBIGE ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-11 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1-3,6-11,14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment received on 09/16/2009, wherein claims 1, 3, 6, and 15 have been amended, and new claim 16 has been added.

Applicant's amendment overcomes the rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being indefinite.

Claims 1-3, 6-11, and 14-16 are examined herein, insofar as they read on the elected invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 11, 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bountra et al. (WO 00/61231, PTO-1449).

Bountra et al. discloses a method of treating multiple sclerosis comprising administering sodium channel antagonists such as 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine called lamotrigine, 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine, and compounds of formula (II) with C1-4 alkyl substituents or CF3 groups. See page 7, lines 20-24; page 8, lines 5-10; page 14, claim 7; page 1, lines 15-19; page 3, lines 9-12. A dose range of sodium channel antagonist is 200 mg/day to 900 mg/day for an adult

human. See page 10, lines 1-8. Bountra et al. also teaches that it may be necessary to make routine variation to the dosage, depending on the age and condition of the patient. See page 10, lines 1-8.

Bountra et al. does not explicitly teach administration of lamotrigine in the method of treating multiple sclerosis i.e does not provide an example.

Bountra et al. does not teach 1, 2, 4-triazine compounds with alkyl substituents such as methyl, ethyl as in claim 16.

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer lamotrigine to treat multiple sclerosis because Bountra et al. teach that sodium channel antagonist such as lamotrigine are useful in treating multiple sclerosis. Accordingly, one of ordinary skill in the art would have been motivated to administer lamotrigine with reasonable expectation of success of treating multiple sclerosis.

Further, regarding the recitations, “wherein the therapy results in reduction of one or more of incidence of relapse, spasticity and fatigue”, “wherein the therapy stabilizes the patients Expanded Disability Status Score, thus halting progress of the disease”, in claims 8-9, since Bountra et al. render the claimed method of administration of effective amounts of lamotrigine for treating multiple sclerosis obvious, administration of lamotrigine necessarily results in reduction of one or more of incidence of relapse, spasticity and fatigue”, halts progress of the disease, as claimed herein.

It would have been obvious to a person of ordinary skill in the art at the time of invention to employ triazine compounds containing alkyl substituents in the method of

treating multiple sclerosis because Bountra et al. teach structurally similar diazine compounds containing C1-4 alkyl substituents, and trifluoromethyl groups as sodium channel blocker, useful in the methods of treating multiple sclerosis. Accordingly, one of ordinary skill in the art at the time of invention would have been motivated to the instant particular triazine compounds containing C1-4 alkyl substituents or trifluoromethyl groups with reasonable expectation of employing them in the method of treating multiple sclerosis.

Claims 10, 14-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bountra et al. (WO 00/61231, PTO-1449) as applied to claims 1-3, 6-9, 11, 16.

Bountra et al. is applied as discussed above.

Bountra et al. discloses a method of treating multiple sclerosis comprising administering sodium channel antagonists such as 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine called lamotrigine, 5-amino-6-[2,3,5-trichlorophenyl]-1,2,4-triazine. See page 7, lines 20-24; page 8, lines 5-10. A dose range of 200 mg/day to 900 mg/day for an adult human is disclosed. Bountra et al. also teaches that it may be necessary to make routine variation to the dosage, depending on the age and condition of the patient. See page 10, lines 1-8.

Bountra et al. does not specifically teach the amount of lamotrigine as 600 mg/day as in claim 14, and the dosing regimen as in claim 15.

It would have been obvious to a person of ordinary skill in the art at the time of invention to determine or optimize parameters such as effective amounts of lamotrigine to be administered in the method of treating multiple sclerosis.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 11, and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lunardi et al. (Neurology, volume 48(6), 1997, pages 1714-1717, PTO-892).

Lunardi et al. discloses administration of lamotrigine to patients suffering from multiple sclerosis in which trigeminal neuralgia was also present. See abstract; page 1715. Lamotrigine was administered at an initial dosage of 25 mg/day, increasing in increments of 25 mg every third day up to a maximum absolute dosage of 400 mg/day. See page 1716, left hand column. Administration of lamotrigine to patients suffering from multiple sclerosis concomitant with trigeminal neuralgia resulted in complete pain relief.

Lunardi et al. does not specifically teach the specific amount of lamotrigine as between 500 mg/day and 700 mg/day.

It would have been obvious to a person of ordinary skill in the art at the time of invention to determine or optimize parameters such as effective amounts of lamotrigine to be administered in the method of treating multiple sclerosis.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Further, regarding the recitations, "wherein the therapy results in reduction of one or more of incidence of relapse, spasticity and fatigue", "wherein the therapy stabilizes the patients Expanded Disability Status Score, thus halting progress of the disease", in claims 8-9, since Lunardi et al. render the claimed method of administration of effective amounts of lamotrigine for treating multiple sclerosis obvious, administration of lamotrigine necessarily results in reduction of one or more of incidence of relapse, spasticity and fatigue", halts progress of the disease, as claimed herein.

Response to Arguments

Applicant argues that "The Action points to Bountra, page 10, lines 1-8. However, this passage is merely a boiler plate disclosure that, for different sodium channel blockers, the physician should take into account the age and condition of the patient. However, this is what the physicians have done in the case of Lunardi in treating multiple sclerosis patients 16-20 with far lower doses of lamotrigine (i.e., 125 mg/day) than other patients (max 400mg/day). Bountra therefore provides more support for encouraging the physician to take account of the patient's condition (multiple sclerosis)

and to use a lower dose accordingly." These arguments have been considered, but not found persuasive. Bountra et al. clearly discloses that sodium channel antagonists which includes lamotrigine are used for treating multiple sclerosis. Contrary to applicant's remarks that Bountra provides more support to use a lower dose, Bountra broadly teaches a dose range of sodium channel antagonists therein which include lamotrigine as 200 mg/day to 900 mg/day for an adult human. It would have been obvious to a person of ordinary skill in the art at the time the invention to determine the effective amounts of lamotrigine employed in the method of treating multiple sclerosis, since the optimization of effective amounts of known agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art, and further Bountra teaches that it may necessary to make routine variations to the dosage. One of ordinary skill in the art at the time of invention would have been motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

Applicant argues that "The Action cites to claim 7 of Bountra as a disclosure that sodium channel blockers may be used to treat multiple sclerosis. Applicants have previously provided reference to the fact that carbamazepine, a sodium channel blocker, makes multiple sclerosis worse (Ramsaransing, et al)." These arguments, and the papers cited by the applicant have been considered, but not found persuasive. Bountra et al. clearly discloses that sodium channel antagonists are used for treating

multiple sclerosis. See page 14, claim 7 of Bountre et al.; page 7, lines 20-24; page 8, lines 5-10. Bountra et al. teaches sodium channel antagonist such as 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine called lamotrigine, as the preferred sodium channel antagonist. It is pointed out that, it has been well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to person of ordinary skill in the art. In re Boe, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966); In re Lamberti, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); In re Fracalossi, 681 F.2d 792, 794, 215 USPQ, 570 (CCPA 1982); In re Kaslow, 707 F.2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983).

Applicant's arguments with respect to side effects have been considered. It pointed out that Guberman et al. teaches that the prescription of lamotrigine, as with all other drugs should be undertaken with appropriate consideration of the potential risks to the patient in relation to potential benefits i.e one needs to exercise caution in using lamotrigine as with any other drug. See page 989 of Guberman et al.

Applicant argues that "Lunardi likewise does not suggest treatment of multiple sclerosis using the claimed dosage level. Thus, taking Bountra alone, or in combination with Lunardi, the physician would not have been motivated to arrive at the presently claimed dosage of between 500mg/day and 700mg/day and, in fact, would have acted to reduce the dosage in the case of multiple sclerosis patients based on the state of the art." These arguments have been considered, but not found persuasive as discussed above. One of ordinary skill in the art at the time of invention would have been

motivated to the particular treatment regimen because the optimization of result effect parameters e.g., dosage range, dosing regimens, dosing duration is obvious as being within the skill of the artisan, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of known ingredients in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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